

Human germline gene editing needs global regulation

COMMUNICATION | EDITORIAL | INVITED CONTRIBUTION | **PERSPECTIVE** | REPORT | REVIEW

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ABSTRACT

The first gene-edited human babies were born in China in late 2018, but no new legislation has been enacted despite widespread outrage. There is a pressing societal need to address the moral and ethical issues associated with germline gene editing before more cases occur. A temporary worldwide moratorium on reproductive germline gene editing should be instituted immediately until such a time as an International Gene Editing Agency is established to develop an enforceable global regulatory framework with broad public engagement. This will, in turn, give us the opportunity to rethink the ethics of heritability in a post-gene editing world.

Introduction

On 25th November 2018, Dr He Jiankui, an associate professor at the Southern University of Science and Technology in Shenzhen, China, released a series of Youtube videos in which he announced the birth of the first gene-edited human babies [1]. Unlike any experiment that came before, Dr He edited the genomes of two single-cell female embryos with the aim to edit every cell in the body. Since this includes the egg and sperm cells, known as germline cells, these edits may be passed down to any future descendants these babies eventually have. In contrast, editing of adult (somatic) cells cannot be passed on to future generations and is therefore isolated in the individual patient [2].

While I was immediately captivated, I was hesitant to publish a response. Surely this was the stimulus that policymakers needed to finally regulate emerging gene editing technologies, so any policy recommendations that I could make would be immediately superseded by an actual proposal. Instead, the worst has come to pass: the news cycle moved on, and few remain talking about the little girls who made history.

To perform this experiment, Dr He used CRISPR, a technology for cutting DNA at precise, customisable locations. While this article focuses on the ethics rather than the science of CRISPR, those unfamiliar with how it works may find a review article about its history and technical specifics helpful [3]. Full details of Dr He's work have not been published, so unfortunately many scientific questions remain unanswered, such as whether

both copies of the genome were edited in every cell as claimed, but the Chinese government has confirmed that the editing did take place [4].

After presenting selected data at the Second International Summit on Human Genome Editing just three days following his announcement, Dr He was met with nearly unanimous criticism by fellow scientists [5, 6]. The next day it was reported by Chinese state media that the Chinese government had suspended his lab's research [7], and his lab website was taken offline. Dr He himself has not spoken publicly since the summit, and he has since been fired by his university and was sentenced to three years in prison for performing 'illegal medical practices' [8].

In Dr He's defence, it was not at all initially obvious that what he did was illegal. Unlike in the UK, where the Human Fertilisation and Embryology Authority (HFEA) explicitly bans germline editing [9], there was no law or regulation specifically banning it in China. Instead, the 'Technical Norms on Human Assisted Reproductive Technologies' published by the Chinese Ministry of Health in 2003 states 'the use of genetically manipulated human [...] embryos for the purpose of reproduction is prohibited' [10]. While this should have dissuaded Dr He, such technical norms are generally unenforceable without being authorised by law, so it was not until this case became a sensation that it was clear that flouting the norm would actually be punishable. Meanwhile, many countries including the United States have no laws regulating this new technology (although the US has banned federal funds from being used for germline editing research) [9].

It is unknown where germline gene editing research will go from here. On one hand, Dr He shows us that a small team of scientists is capable of performing a germline gene edit on a human embryo resulting in a live birth. Over the past year, Dr Denis Rebrikov at the Pirogov Medical University in Moscow has also been vocal about performing similar edits on human embryos—although he claims he will not implant them until he gains regulatory approval [11]. On the other hand, the vilification that Dr He has received will hopefully deter the majority of scientists from repeating his work, and, at present, the expertise and resources required to perform this feat are a sufficient hurdle to prevent non-

scientists from trying to replicate it. However, there is a real possibility that research will be done in secret or that future advancements will remove technical barriers to entry, so the time is ripe to act on a global scale to regulate germline gene editing.

Available Policy Pathways

We are at a crossroads with four paths forward: we could deregulate germline gene editing by either repealing or choosing not to enforce existing regulations, we could ban it entirely, we could fracture into a patchwork of national regulations with no global cohesion, or we could work to determine a single path forward as a species. While it is the most difficult, I see the final option as the only viable scenario in the long term. However, there are still many traps that must be avoided, and I will seek to both justify this belief and outline what it might take to bring it about.

At the dawn of the modern genetic era, the 1975 Asilomar Conference on Recombinant DNA Molecules recognised that unrestricted manipulation of DNA in the lab presents many unknown risks, and, in the absence of laws, scientists resolved to set restrictions on themselves [12]. For over forty years, this voluntary self-regulation has been the norm for much of biotechnology, especially in the US, but this should only be seen as a stopgap and not a permanent solution.

There are numerous technical risks for both individuals and the species should germline gene editing go ahead unchecked: CRISPR is relatively inefficient, often successfully editing only a small percent of cells, and it can also cause off-target mutations, where it cuts DNA at the wrong location, which could cause cancer or any number of genetic diseases [13]. However, the field of gene editing moves fast. New research is published daily in this highly competitive and lucrative field, such as one study detailing how to design CRISPR edits to reduce the chance of off-target effects [14] and a recent clinical trial demonstrating the safety and feasibility of using CRISPR-edited immune cells to target cancer [15].

There is good reason to be hopeful that the technical problems with CRISPR will be fixed, but the

ethical concerns are much more complex. There is no clear line between eliminating a genetic disease and enhancing a desired trait; the same gene that causes muscular dystrophy when lost could increase physical strength if amplified [16]. Additionally, the US allows patenting of both the editing technology and the edits themselves, which grants the companies developing them immense power over their implementation. One needs only to look at the price of prescription drugs in a for-profit market to see that access to any gene editing technology developed by private companies would be restricted to only the wealthiest. A report published by Goldman Sachs last year states ‘given the possible one-time curative nature of gene therapy, we believe price tags of \$1mn+ [per patient] are likely’ [17]. Such a price would be inaccessible for the vast majority of patients and would stretch social healthcare systems beyond many of their capacities.

Moreover, tampering with the natural human gene pool is inherently a major risk in the long term. Differences in environments and cultural ideals (e.g., beauty standards) could lead to the promulgation of different traits in different populations far faster and more effectively than the existing mode of sexual selection, which could fracture humanity into various subspecies over time or put unedited individuals at a social disadvantage. Additionally, homogenization of human genetics could reduce diversity and resistance to infectious diseases. Similarly, we know that planting only one variety of crop makes a field more prone to disease than planting crops with more genetic variation [18]. The risks of germline editing are simply too great to allow a *laissez-faire* approach.

Technological advancements cannot inform our morality, and likewise CRISPR cannot tell us whether we want to direct human evolution or how. It is my personal belief that we are simply not ready as a society or a species for germline gene editing, and if or when we do allow it, it should be a conscious collective decision after suitable scrutiny, education, and debate rather than an individual deciding to pursue it simply because they can.

However, the potential for misuse does not make gene editing itself immoral. CRISPR is an incredibly powerful research tool which has rev-

olutionised biology, allowing scientists unprecedented ability to manipulate the genetics of cell and animal models. This has opened doors for the discovery of novel pharmaceuticals and gene interactions via whole genome CRISPR screens, and new variants of CRISPR can, among other things, transiently affect gene expression without permanently altering the DNA [3].

Applications in adult (somatic) cells also promise to translate CRISPR to human health in untold ways. From curing chronic diseases to eliminating mutated cancer cells with pinpoint accuracy, several such treatments are starting to make their way to patients and showing promising results [15, 19]. No matter one’s objections to germline editing, it is difficult to justify accepting the status quo of congenital diseases when so many could be cured in the individual by somatic gene therapies or prevented entirely by existing genetic counselling practices coupled with limited and precise germline edits. In order to reap these benefits, fundamental research and somatic clinical applications should be enthusiastically supported, and a complete ban on gene editing or even a permanent ban on just germline editing should not be pursued.

Our current situation, and the most likely scenario for the near future, is that each country will form its own policies to regulate gene editing as they have done with fertility treatments, stem cell therapies, and other medical procedures [20]. This has worked in the past and should work for somatic gene editing, since treatments are confined to the individual patient. However, once a germline gene edit enters the gene pool, the only way it can be removed is if none of the carriers have children, or at least if none of these children receive any edited chromosomes. Should any country allow widespread germline gene editing, nothing short of completely closing them off from the rest of the world would prevent comingling of edited and unedited populations. A hypothetical genetic edit should not deprive a person of basic human rights, so any program of compulsory genotyping, labelling of gene-edited individuals, or limiting of reproductive rights should be immediately rejected. And even should such draconian measures be put in place, they would be ineffective; every generation acquires numerous new random mutations in their

genomes which are afterwards indistinguishable from most targeted edits. Therefore, a germline editing ban—or even limits and regulations—in a single country but not the world is effectively meaningless.

Policy Recommendations

So, if a single path forward is the best option, what should it be? Any policy must be both global and enforceable to be effective; therefore, a binding international treaty should be immediately pursued to:

1. impose a temporary, 5-year moratorium on human germline gene editing, until such time as
2. an International Gene Editing Agency can be established and enact initial regulations. This agency would also be empowered to act as a watchdog.

This approach may appear reminiscent of a failed attempt in the early 2000's to ban human cloning via treaty, where a lack of real urgency and vague technical language resulted instead in a non-binding declaration [21]. A similar fate befell a Convention on Human Rights and Biomedicine proposed to the Council of Europe in the late 1990s [22], and both resulted in a patchwork of national regulation. Instead, if it had been announced that human cloning was actively ongoing, countries seeking a full ban would likely have compromised for some restrictions, and likewise had the treaty included a sunset clause, it likely would have placated the countries that were against a full ban. UNESCO has also published declarations on bioethics [23], but they too suffer from unenforceability. Instead of adding enforcement to the broad scope of UNESCO's Constitution, establishing an independent organisation will provide greater transparency, efficacy, and manoeuvrability.

The International Atomic Energy Agency serves as a particularly useful model, as they are invested with the power to issue standards and perform inspections ensuring the safety of nuclear power and preventing the proliferation of nuclear weapons while also operating autonomously from the UN. Although it would be significantly

more difficult to detect germline gene editing than atomic bombs, independent audits of reproductive therapy providers and research funding portfolios would be widely effective, coupled with public outreach to encourage reporting of rogue actors. Additionally, China's strong response to Dr He's work suggests that there is the political will for individual states along with the UN to isolate and sanction those that refuse to subscribe to the regulations in a manner comparable to nations in violation of the Treaty on the Non-Proliferation of Nuclear Weapons. In this way, we may not prevent all cases of germline editing, but we can prevent it from becoming mainstream while also providing a mechanism to permit certain applications in the future.

This recommendation builds on previous calls for a global gene editing observatory [24]. Jasanoff and Hurlbut envision the establishment of new institutions for careful deliberation across professional and national boundaries, but it is now clear that there is an urgent need for action while policymakers can come to terms with the details—therefore, a temporary moratorium on germline editing while the Agency is created. And while their proposed observatory would be an ideal model for determining the rules for CRISPR moving forward, it lacks power and must be coupled with a mechanism of enforcement—therefore, the establishment of the proposed Agency.

In an apparent attempt to get out ahead of the backlash, Dr He published a list of principles for regulating human germline gene editing just before his announcement [25], such as 'only for serious disease, never vanity,' and 'wealth should not determine health.' This article has since been retracted by the journal, but it offers a glimpse into the reasoning Dr He used to justify his work. In fact, his recommendations would have been useful if we lived in a world in which germline gene editing was broadly accepted, but that is simply not the case, and the risks of implementation on a global scale have not been properly evaluated. Dr He clearly miscalculated how hostile the response to his news would be, and as a result these suggestions have been largely lost in the noise.

I cannot say exactly what specific regulations should be made, and neither is it any individual's place to dictate what these regulations should be.

Instead, it is the responsibility of everyone in a society to say what they want in order to determine policy, via a concept coined by Jasanoff called civic epistemology, or the ‘stylized, culturally-specific ways in which publics expect the state’s expertise, knowledge, and reasoning to be produced, tested, and put to use in decision making’ [20]. While the proposed Agency provides a vessel for making and enforcing regulations, we must decide together how to fill it. We therefore face the enormous task of synthesising our various culture-specific epistemologies into a single new one as a species.

A Brave New World?

CRISPR technology fundamentally changes our understanding of heritability and of what it means to be human. Before, it was impossible to separate the genome from the individual or to conceive of a way to design or alter the genetic code of one’s offspring. The entire concept of familial heritage is intimately connected to the assumption that your genome is unique, inalienable, and, to put it simply, yours to begin with. How, then, can the ethics derived before gene editing carry over? Instead, we should see the development of germline gene editing as an opportunity to re-examine how we conceive human evolution.

Genetic variation is necessary for evolution to occur; we must then decide whether to end the evolution of humanity by eliminating variation, whether to allow it to proceed as the slow and random process it has for the history of life, or whether to accelerate it deliberately through genetic intervention. As this is a monumental decision, it should not be made hastily and certainly not by a privileged few. Instead, scientists must seek to effectively communicate with and educate everyone about the possibilities of gene editing as they develop, and perhaps someday the proposed Agency can be replaced with ongoing global referenda with equal, universal suffrage to determine our course forward.

Two years before Asilomar, science fiction writer Robert A. Heinlein predicted a future of uninhibited genetic editing. When the protagonist of the novel is cloned (and these clones genetically edited) without his knowledge, he reasons

‘You don’t own your genes—nobody does. Genes belong to the race; they’re simply lent to the individual for his-her lifetime’ [26]. Heinlein’s vision should scare us, but there is perhaps some truth to his reasoning. We should think of our genetics as a Commons that we all share and all must protect, and rather than assigning different values to certain genetic varieties as ‘good’ or ‘bad’, we should realise that all DNA has the same value. We may recognise that specific mutations which lead to disease are detrimental, but even these do not alter the moral worth of the DNA or of the individual who is ‘borrowing’ it from the species. Instead, it is the depth of the gene pool that is our strength as a species, and in order to be good stewards of the human genome, we must actively restrain and refocus the use of this powerful technology in a manner that is democratic—and never plutocratic or eugenic. We all have a share in this, so we all deserve a say.

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Conflict of interest The Author declares no conflict of interest.